Sialylated therapeutic IgG: a sweet remedy for inflammatory diseases?*

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Introduction

Immunoglobulin G (IgG) is the main serum glycoprotein responsible for detection and destruction of pathogens or their noxious products. IgG consists of Fab (‘fragment antigen binding’) regions, that recognize antigenic targets and provide diversity to antibodies, and Fc (‘fragment crystallizable’) regions, that allow antibodies to interact with Fc gamma receptors (FcγR) on phagocytes (Fig. 1). Currently, four classes of FcγR are identified: FcγRI, FcγRII, FcγRIII and FcγRIV [1]. For the initiation of a biological response against the bound antigen, IgGs rely on their constant Fc portion. CH2 domains of the Fc fragment contain complex oligosaccharide structures covalently attached to asparagine 297 of the heavy chain of the IgG [2,3]. The presence of a complex oligosaccharide structure modulates the functions of IgG, especially the activation of complement and binding to FcγR [4]. The monosaccharide content of the complex oligosaccharides in antibodies, including monoclonal IgGs (MAbs), is highly variable. More than 30 different glycoforms linked to Fe have been described [4]. The impact of the carbohydrate structure on the biological functions of IgGs remains unresolved.

Overview of the study by Kaneko et al. [5]

The study by Kaneko et al. [5] sheds light on the role of the sialic acid-terminating glycan structures on the biological activities of IgG. The authors have compared the properties of IgG with a higher content of sialic acid to those with a lower content. They demonstrate that highly sialylated forms of monoclonal mouse IgGs have reduced affinity for FcγR and cytotoxic function. Furthermore, the authors demonstrate that the anti-inflammatory activity of the therapeutic human immunoglobulin G (IVIg) is mediated mainly by a fraction of antibodies with terminal sialic acid on their oligosaccharide structures. The IVIg fraction enriched in sialic acid-containing antibodies showed an FcγRIIB-dependent stronger protective effect, while the enzymatic removal of the sialic acid residues abrogated the anti-inflammatory activity of IVIg in a mouse model of rheumatoid arthritis [5]. Using nephrototoxic serum nephritis model, Kaneko et al. also demonstrate that the content of sialic acid in IgG varies during the evolution of the immune responses against antigens. At later stages of the response, during the process of affinity maturation, IgG antibodies switch to variants that lack sialic acid in their oligosaccharide structures.

Discussion

Several studies have investigated the influence of the glycan composition on the effector functions of IgG. Using the same clone of the recombinant therapeutic anti-human CD20 mouse/human chimeric IgG1 rituximab, it has been demonstrated that the effector activity of the IgG1 depends strongly on the content of fucose in the glycans [6]. Thus, IgG containing non-fucosylated complex oligosaccharides show a substantially greater affinity for binding to FcγRIIIA and induce a stronger antibody-dependent cellular cytotoxicity (ADCC). As the therapeutic activity of rituximab is mainly due to ADCC, these results have obvious clinical significance. In addition, the presence of α2,3-linked sialic acid in the glycans...
of human IgG3 have a profound inhibitory effect on complement- and on FcγR-dependant effector functions [7]. Furthermore, a higher level of sialylation of monoclonal IgG antibodies leads to a decrease in its binding to FcγRIIIA and a considerable reduction of their ADCC activity [8]. These findings together with the results obtained by Kaneko et al. implicate an important role for sialic acid in modifying the
biological functions of IgG. Monitoring the sialylation of disease-associated IgG antibodies during different phases of an antibody-mediated disease may have a diagnostic and prognostic potential.

Similar to highly sialylated IgG, IgG exposed to reactive oxygen species has a weaker binding to Fcγ receptors [9]. In addition, oxidized IVIg has an enhanced anti-inflammatory activity and protects mice from experimental sepsis [10].

Initially used as replacement therapy in primary and secondary immune deficiencies, IVIg is also widely used for the treatment of a number of autoimmune and systemic inflammatory diseases [11,12]. The mechanisms of action of IVIg are multiple and mutually non-exclusive [11,13–16]. Some of the mechanisms depend on the interaction between the Fc portion of IVIg and FcγR on target cells. Others rely on the variable regions of antibodies. Thus, IVIg represents a very complex and stochastic system, built from microfractions with different (sometimes opposite) immunomodulatory effects. Therefore, some of these microfractions of antibodies may quench the biological effect of others. It is possible to isolate or enrich a fraction of antibodies with particular specificities such as idiotypic determinants, cell-surface molecules including Fas, integrins, CD4, HLA and CD40 [11,17].

Perspective

IgGs can mediate pro- and anti-inflammatory activities through the engagement of Fc with distinct FcγR. The finding that sialylation of Fc portion of an antibody can determine anti-inflammatory properties provides new opportunities for enhancing the efficacy of current therapeutic immunoglobulins and for the development of new therapeutics. Thus the therapeutic efficacy of MAbs may be optimized by the selection of a glycoform that is best suited. As the current generation of licensed therapeutic MAbs bear oligosaccharides essentially devoid of sialic acid [18], the study by Kaneko et al. [5] may not find an application for the improvement of existing MAbs. However, sialylation of Fc has to be considered while developing new therapeutic MAbs.

The infusion of purified Fc fragments of IVIg ameliorates acute immune thrombocytopenic purpura in children and in murine models, similar to IVIg [13,19]. Kaneko et al. [5] demonstrate that sialylation of the Fc portion confers Fc-mediated anti-inflammatory properties to IVIg in experimental models. Thus, sialic acid-enriched IVIg preparations might prove a better therapeutic option. Alternatively, considering the cost involved in additional fractionation steps for enriching sialylated IgG, recombinant sialylated Fc fragments of IgG could be an attractive therapeutic alternative that could contribute to overcoming the shortage of IVIg for several autoimmune diseases [20]. Since the Fc moiety is not diversified as Fab fragments, producing recombinant therapeutic Fc fragments should be a plausible task in the shorter term. However, there is a lack of correspondence between IgG subclasses and Fc receptors in human and mice, and hence the phenomenon described by Kaneko et al. needs to be carefully investigated in humans.

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